claims 22 and 23 is found within the specification (e.g., original claims 1-16, and 20; figures 2 and 4). Accordingly, the subject matter of claims 22 and 23 also does not constitute new matter.

Applicants respectfully submit that addition of new claims 22-23 should not provoke an additional restriction requirement because the new claims are drawn to methods and kits for detecting compounds that modulate topoisomerase activity. Accordingly, these claims fall within elected Group I of the restriction requirement mailed March 26, 2002.

The 35 U.S.C. § 102 Rejection of the Claims

The Examiner has rejected claims 1-16 and 20 under 35 U.S.C. § 102(e) alleging that Lynch et al. (U.S. Patent 6,197,527 B1) inherently discloses an assay for nucleic acid religation. Applicants respectfully traverse this rejection.

Claim 1 provides to a high-throughput method of screening compounds capable of modulating topoisomerase activity comprising, incubating at least a first nucleic acid, a topoisomerase and a potential topoisomerase-modulating compound, wherein the nucleic acid comprises at least one tag, and assaying for a nucleic acid religation product.

Claim 20 provides a kit for screening for compounds that modulate topoisomerase religation activity comprising: (a) a substrate nucleic acid comprising a first tag, (b) a religation nucleic acid comprising a second tag and a 5'-OH, (c) a topoisomerase, and a means for measuring a covalently linked product comprising (a) and (b) in a test mixture comprising (a), (b) and (c) in the presence or absence of a topoisomerase-modulating compound.

In order to anticipate a claimed article, a reference must clearly convey to one skilled in the art that the article has been invented. *In re Schaumann*, 197 U.S.P.Q. 5 at 8 (C.C.P.A. 1978). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Dillon*, 919 F.2d 688, 16 USPQ 2d 1897, 1908 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the

defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Moreover, an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply as a possible conclusion, from the teaching of the cited art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Lynch et al. concerns methods for detecting topoisomerase inhibitors using either a solid-phase or a liquid-phase method. The detection step disclosed by Lynch et al. is based on inhibition of the topoisomerase activity such that once a break in DNA has been introduced by the topoisomerase, the topoisomerase becomes trapped in a complex with the nucleic acid substrate such that no religation and release of the topoisomerase can occur. Lynch et al. discloses directly detecting the topoisomerase that is complexed to a nucleic acid substrate or indirectly detecting a nucleic acid that is not religated. See, for example, U.S. Patent 6,197,527 B1 col. 2, lines 6-44 and Figures 1-4.

Applicants submit that for the solid phase assays, not only does Lynch et al. fail to disclose the step of detecting nucleic acid religation, the assays as carried out, render religation an impossibility. The topoisomerase when complexed with a nucleic acid substrate is contacted with a denaturant prior to detection. Such a denaturant would necessarily prevent the topoisomerase enzyme from religating nucleic acids. U.S. Patent 6,197,527 B1 col. 4, lines 47-52; see also Figures 1-4; col. 3, lines 29-31; col. 8, lines 38-41; col. 8, lines 51-56; col. 16, lines 50-53. Not only does Lynch et al. fail to disclose detecting religation, but religation cannot flow as a necessary conclusion as it is actively prevented, thus Lynch et al. cannot anticipate the claimed invention.

Moreover, even if religation was possible, its occurrence could not be distinguished from the result produced by an inactive topoisomerase or a modulator that inhibits the binding of topoisomerase to the substrate nucleic acid. In all these situations, there would be no topisomerase complexed to nucleic acid and no detectable signal would be generated. Thus,

Lynch et al. cannot inherently anticipate the claimed invention, as religation does not flow as a necessary conclusion in the absence of a detectable trapped topoisomerase.

In the liquid phase assays described in Lynch et al., at columns 17-20, two labels present on a substrate nucleic acid are positioned in proximity such that emission from one of the labels is quenched by the proximity of the other label. A detectable emission signal is generated when the two labels present on a substrate nucleic acid are separated as a topoisomerase cleaves the nucleic acid substrate between the labels, but cannot religate as the presence of a modulator or inhibitor traps the topoisomerase in a covalent complex with the nucleic acid. However, religation of a cleaved nucleic acid fragment cannot be distinguished from the absence of any topoisomerase activity on the original nucleic acid substrate. This could be the result of an inactive topoisomerase or a modulator that inhibits the binding of topoisomerase to the substrate nucleic acid. These three events would be indistinguishable as they would all produce a quenched signal, as the labels would be in the same proximity as in the original substrate. Hence, one of skill in the art could not determine whether the topoisomerase employed was non-functional, whether a modulator in the reaction mixture was an inhibitor of topoisomerase that prevented the initial binding of the topoisomerase to the substrate nucleic acid or whether the modulator was ineffective and religation had occurred. Therefore, any conclusion that Lynch et al. is inherently assaying for religation does not flow as a necessary conclusion from the disclosed assay results. Instead, religation is simply a possible conclusion that cannot be distinguished from several others. Thus, Lynch et al. does not anticipate the claimed invention.

The Examiner has also asserted that Lynch et al. describe a second nucleic acid that is allegedly a religation strand comprising oligonucleotides operatively associated with at least one marker tag (citing col. 16, line 67 to col. 17, line 26). See Official Action mailed June 12, 2002 at page 4. However, this text merely discloses an alternative way to detect an immobilized topoisomerase-nucleic acid complex where a second nucleic acid can hybridize to the complexed first nucleic acid (column 17, lines 3-10). Lynch et al. does not disclose or suggest that the first and second nucleic acids are re-ligated, i.e. covalently linked, by a topoisomerase. In fact, Lynch et al. disclose that the second nucleic acid is used as a label after a denaturant is added to stabilize the nucleic acid-topoisomerase complex (column 16, lines 50-53). Such denaturation

would prevent the denatured topoisomerase from covalently linking the first and second nucleic acids. Accordingly, Lynch et al. does not describe a religation strand or a religation product.

The Examiner has also asserted that Lynch et al. describes a high-throughput method wherein the nucleic acid and topoisomerase are covalently complexed and wherein the topoisomerase retains religation activity (citing column 15, lines 11-15 and Figure 1). See Official Action mailed June 12, 2002 at page 5. Again, a denaturant is added to stabilize the nucleic acid-topoisomerase complex and would result in a denatured topoisomerase that could not perform religation. Accordingly, Lynch et al. do not describe a topoisomerase that retains religation activity.

In conclusion, the Examiner has failed to establish anticipation either explicitly or by inherency because Lynch et al. disclose that either religation cannot occur, or if religation does occur, it cannot be distinguished from other possible events involving the topoisomerase. Hence, Lynch et al. does not anticipate the claimed subject matter, and Applicants respectfully request withdrawal of this rejection of the claims under 35 U.S.C. § 102(e).

Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney (516-795-6820) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: *The undersigned hereby certifies that this correspondence is being deposited with the United States Postal* Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 12th day of November, 2002.

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